AMENDMENT

Amendments to the Claims

1. (currently amended) A ~~composition comprising a~~ phospholipid nanovesicle incorporating a polypeptide comprising

an inner leaflet component, wherein the inner leaflet component is a phospholipid selected from the group consisting of phosphatidylserine, phosphatidylethanolamine~~,~~ and structural analogs thereof, a prosaposin-related polypeptide, wherein the polypeptide has an amino acid sequence selected from the group consisting of:

the polypeptide has an amino acid sequence selected from the group consisting of the amino acid sequence set forth in SEQ ID NO:1, the amino acid sequence set forth in SEQ ID NO:1 having one or more conservative substitutions, the amino acid sequence set forth in SEQ ID NO:2, and the amino acid sequence set forth in SEQ ID NO:2 having one or more conservative substitutions; and a pharmaceutically acceptable carrier;

wherein the prosaposin-related polypeptide retains plasma-membrane affinity;

wherein the nanovesicle has an average diameter in the range of 10 to 800 nm; and

wherein the nanovesicle exhibits anti-tumor activity

~~(a) the amino acid sequence set forth in SEQ ID NO:1;~~

~~(b) an amino acid sequence substantially identical to the amino acid sequence set forth in SEQ ID NO:1 having at least 95% sequence identity to the amino acid sequence set forth in SEQ ID NO:1, wherein said polypeptide comprises a biologically active portion of a prosaposin polypeptide comprising at least 25 contiguous amino acids present in a prosaposin polypeptide and retains plasma-membrane affinity;~~

~~(c) the amino acid sequence set forth in SEQ ID NO:2; and~~

~~(d) an amino acid sequence substantially identical to the amino acid sequence set forth in SEQ ID NO:2 having at least 95% sequence identity to the amino acid sequence set forth in SEQ~~

~~ID NO:2, wherein said polypeptide comprises a biologically active portion of a saposin polypeptide comprising at least 25 contiguous amino acids present in a saposin polypeptide and retains plasma-membrane affinity and a pharmaceutically acceptable carrier;~~

~~wherein the percentage of sequence identity is determined by a sequence comparison program equivalent to the GCG program GAP (Version 10.00 or later) wherein the comparison window is at least 20 contiguous amino acids in length; and~~

~~wherein the prosaposin related polypeptide and the inner leaflet component are contacted with an acidic buffer and treated together to form a nanovesicle exhibiting anti-tumor activity~~.

2. (previously presented) The composition of claim 1, wherein the inner leaflet component is phosphatidylserine or a structural analog thereof.

3. (previously presented) The composition of claim 2, wherein said phosphatidylserine or structural analog thereof is selected from the group consisting of phosphatidic acid, phosphatidylglycerol, phosphatidylinositol, palmitoyloleoylphosphatidylserine, palmitelaidoyloleoylphosphatidylserine, myristoleoyloleoylphosphatidylserine, dilinoleoylphosphatidylserine, palmiticlinoleoylphosphatidylserine, lysophosphatidylserine, and dioleoylphosphatidylserine.

4. (previously presented) The composition of claim 1, wherein the molar ratio of polypeptide to phospholipid is in the range from about 1:1 to about 1:50.

5. (previously presented) The composition of claim 2, wherein the molar ratio of prosaposin-related polypeptide to phospholipid is in the range from about 1:1 to about 1:10.

6. (previously presented) The composition of claim 1 wherein the composition is capable of inducing apoptosis in hyper-proliferating cells.

7. (previously presented) The composition of claim 1, wherein the biologically active portion of prosaposin polypeptide comprises at least 80 contiguous amino acids present in the prosaposin-related polypeptide.

8. (previously presented) The composition of claim 7, wherein the mass ratio of the polypeptide to the inner leaflet component is in the range from about 15:1 to about 3:10.

9. (withdrawn) A method for modulating the distribution of an inner leaflet component in a plasma membrane of a cell of a subject comprising administering to said subject a therapeutically effective amount of the agent of claim 1.

10. (withdrawn) The method of claim 9, wherein said inner leaflet component is phosphatidylserine or a structural analog thereof.

11. (withdrawn) The method of claim 10, wherein said phosphatidylserine or structural analog thereof is dioleoylphosphatidylserine.

12. (withdrawn) The method of claim 9, wherein the distribution of said inner leaflet component in the outer leaflet of said plasma membrane is altered.

13. (withdrawn) The method of claim 12, wherein the concentration of said inner leaflet component in said outer leaflet is increased.

14. (withdrawn) The method of claim 9, wherein the distribution of said inner leaflet component is modulated in hyper-proliferating cells.

15. (withdrawn) The method of claim 14, wherein said hyper-proliferating cells are selected from the group consisting of tumor cells and cancer cells.

16. (withdrawn) The method of claim 9, wherein said method promotes cell death.

17. (withdrawn) A method of modulating tumor volume in a subject, said method comprising administering a therapeutically effective amount of the agent of claim 1.

18. (withdrawn) The method of claim 17, wherein said agent promotes cell death in hyper- proliferating cells.

19. (withdrawn) The method of claim 18, wherein said hyper-proliferating cells are selected from the group consisting of tumor cells and cancer cells.

20. (withdrawn) The method of claim 19, wherein said cancer cells are selected from the group consisting of sarcoma, neuroblastoma, breast carcinoma, and squamous cell

carcinoma cells.

21. (withdrawn) The method of claim 17, wherein said inner leaflet component is phosphatidylserine or a structural analog thereof.

22. (withdrawn) The method of claim 21, wherein said phosphatidylserine or structural analog thereof is dioleoylphosphatidylserine.

23. (withdrawn) The method of claim 17, wherein said subject is a mammal.

24. (withdrawn) The method of claim 23, wherein said mammal is a human.

25. (withdrawn) The method of claim 17, wherein said tumor volume decreases.

26. (withdrawn) The method of claim 17, wherein the molar ratio of said polypeptide to said inner leaflet component is in the range from about 1:1 to about 1:50.

27. (withdrawn) The method of claim 26, wherein the molar ratio of said polypeptide to said inner leaflet component is in the range from about 1:1 to about 1:10.

28. (withdrawn) The method of claim 17, wherein said agent further comprises a pharmaceutically acceptable carrier.

29. (withdrawn) A method of treating a cancer in a subject, said method comprising administering a therapeutically effective amount of the agent of claim 1.

30. (withdrawn) The method of claim 29, wherein said inner leaflet component is phosphatidylserine or a structural analog thereof.

31. (withdrawn) The method of claim 30, wherein said phosphatidylserine or structural analog thereof is dioleoylphosphatidylserine.

32. (withdrawn) The method of claim 29, wherein the molar ratio of said polypeptide to said inner leaflet component is in the range from about 1:1 to about 1:50.

33. (withdrawn) The agent of claim 32, wherein the molar ratio of said polypeptide to said inner leaflet component is in the range from about 1:1 to about 1:10.

34. (withdrawn) The method of claim 29, wherein said agent further comprises

a pharmaceutically acceptable carrier.

35. (withdrawn) The method of claim 29, wherein said agent promotes cell death in hyper-proliferating cells.

36. (withdrawn) The method of claim 35, wherein said cell death occurs through apoptosis.

37. (withdrawn) The method of claim 35, wherein said hyper-proliferating cells are selected from the group consisting of cancer cells.

38. (withdrawn) The method of claim 37, wherein said cancer cells are selected from the group consisting of sarcoma, neuroblastoma, breast carcinoma, and squamous cell carcinoma cells.

39. (withdrawn) The method of claim 29, wherein said subject is a mammal.

40. (withdrawn) The method of claim 39, wherein said mammal is a human.

41. (withdrawn) The method of claim 29, wherein said agent is administered enterally, parenterally, subcutaneously, intravenously, intraperitoneally, or topically.

42. (withdrawn) The method of claim 29, wherein multiple doses of said agent are administered to said subject.

43. (withdrawn) The method of claim 29, wherein a single dose of said agent is administered to said subject.

44. (currently amended) An anti-tumor composition comprising a nanovesicle prepared by the process of claim 64, wherein the polypeptide ~~having~~ has the amino acid sequence set forth in SEQ ID NO:2, wherein the inner leaflet component is dioleoylphosphatidylserine and ~~a pharmaceutically acceptable carrier; wherein the polypeptide and the dioleoylphosphatidylserine form a nanovesicle; and~~ wherein the composition is capable of inducing apoptosis in hyper-proliferating cells ~~wherein the prosaposin related polypeptide and the inner leaflet component are contacted with an acidic buffer and treated together to form a nanovesicle exhibiting anti-tumor activity~~.

45. (previously presented) The anti-tumor composition of claim 44, wherein the mass ratio of polypeptide to dioleoylphosphatidylserine is approximately 5:1.

46. (previously presented) The anti-tumor composition of claim 44, wherein the mass ratio of polypeptide to dioleoylphosphatidylserine is approximately 15:7.

47. (previously presented) The anti-tumor composition of claim 44, wherein the mass ratio of polypeptide to dioleoylphosphatidylserine is in the range from about 15:1 to about 3:10.

48. (previously presented) The anti-tumor composition of claim 44, comprising approximately 10 μM polypeptide and approximately 30 μM dioleoylphosphatidylserine.

49. (previously presented) The anti-tumor composition of claim 44, comprising approximately 10 μM polypeptide and approximately 70 μM dioleoylphosphatidylserine.

50. (currently amended) A composition consisting essentially of an inner leaflet component, wherein the inner leaflet component is a phospholipid selected from the group consisting of phosphatidylserine, phosphatidylethanolamine, and structural analogs thereof, a biologically active prosaposin-related polypeptide; and a pharmaceutically acceptable carrier; wherein the prosaposin related polypeptide and the inner leaflet component are ~~reontacted~~ contacted with an acidic buffer and treated together to form a nanovesicle exhibiting anti-tumor activity.

51. (previously presented) The composition of claim 50, wherein the leaflet component is phosphatidylserine or a structural analog thereof.

52. (previously presented) The composition of claim 51, wherein the phosphatidylserine or structural analog thereof is selected from the group consisting of phosphatidic acid, phosphatidylglycerol, phosphatidylinositol, palmitoyloleoylphosphatidylserine, palmitelaidoyloleoylphosphatidylserine, myristoleoyloleoylphosphatidylserine, dilinoleoylphosphatidylserine, palmiticlinoleoylphosphatidylserine, lysophosphatidylserine, and dioleoylphosphatidylserine.

53. (previously presented) The composition of claim 51, wherein the molar ratio of polypeptide to inner leaflet component is in the range from about 1:1 to about 1:50.

54. (previously presented) The composition of claim 51, wherein the molar ratio of polypeptide to inner leaflet component is in the range from about 1:1 to about 1:10.

55. (previously presented) The composition of claim 51 wherein the composition is capable of inducing apoptosis in hyper-proliferating cells.

56. (previously presented) The composition of claim 51, wherein the polypeptide is a biologically active portion of prosaposin polypeptide and retains plasma-membrane affinity.

57. (previously presented) The composition of claim 56, wherein the mass ratio of the polypeptide to the inner leaflet component is in the range from about 15:1 to about 3:10.

58. (new) A process for the manufacture of a pharmaceutical composition comprising the steps of:

(a) combining a composition comprising (i) an inner leaflet component, wherein the inner leaflet component is a phospholipid selected from the group consisting of phosphatidylserine, phosphatidylethanolamine and structural analogs thereof and (ii) a prosaposin-related polypeptide;

wherein the polypeptide has an amino acid sequence selected from the group consisting of the amino acid sequence set forth in SEQ ID NO:1, a biologically active variant of the amino acid sequence set forth in SEQ ID NO:1, the amino acid sequence set forth in SEQ ID NO:1 having one or more conservative substitutions, the amino acid sequence set forth in SEQ ID NO:2, a biologically active variant of the amino acid sequence set forth in SEQ ID NO:2, and the amino acid sequence set forth in SEQ ID NO:2 having one or more conservative substitutions and wherein the polypeptide retains plasma-membrane affinity;

in a pharmaceutically acceptable carrier;

(b) treating the suspension of inner leaflet component and prosaposin-related polypeptide to form a nanovesicle;

wherein the nanovesicle formed exhibits anti-tumor activity.

59. (new) A pharmaceutical composition comprising nanovesicles prepared by the process of claim 58.

60. (new) The pharmaceutical composition of claim 59, wherein the polypeptide has an amino acid sequence selected from the group consisting of the amino acid sequence set forth in SEQ ID NO:1, the amino acid sequence set forth in SEQ ID NO:1 having one or more conservative substitutions, the amino acid sequence set forth in SEQ ID NO:2, and the amino acid sequence set forth in SEQ ID NO:2 having one or more conservative substitutions.

61. (new) The pharmaceutical composition of claim 60, wherein the inner leaflet component is phosphatidylserine or a structural analog thereof.

62. (new) The pharmaceutical composition of claim 61, wherein the molar ratio of polypeptide to phospholipid is in the range from about 1:1 to about 1:50.

63. (new) The pharmaceutical composition of claim 62, wherein the nanovesicle has a diameter in the range 0.01 to 1 μm.

64. (new) A process for the manufacture of a pharmaceutical composition comprising the steps of:

(a) combining a composition comprising (i) a dried inner leaflet component, wherein the inner leaflet component is phosphatidylserine or a structural analog thereof and (ii) a dried and isolated prosaposin-related polypeptide;

wherein the polypeptide has an amino acid sequence selected from the group consisting of the amino acid sequence set forth in SEQ ID NO:1, the amino acid sequence set forth in SEQ ID NO:1 having one or more conservative substitutions, the amino acid sequence set forth in SEQ ID NO:2, and the amino acid sequence set forth in SEQ ID NO:2 having one or more conservative substitutions and wherein the polypeptide retains plasma-membrane affinity;

wherein the molar ratio of the polypeptide to the inner leaflet component in the composition is in the range from 1:1 to 1:25;

in a pharmaceutically acceptable carrier;

(b) treating the suspension of inner leaflet component and prosaposin-related polypeptide to form a nanovesicle;

wherein the nanovesicle formed has a diameter in the range 10 to 800 nm and exhibits anti-tumor activity.

65. (new) A pharmaceutical composition comprising nanovesicles prepared by the process of claim 64.